REMARKS

Reconsideration and allowance are respectfully requested.

Claims 23, 33-41, 44 and 49-54 are pending. The amendments are supported by the original disclosure and, thus, no new matter is added by their entry.

Non-elected claims 33-36, 40-41 and 49-54 were withdrawn from consideration by the Examiner. Applicants request rejoinder of the withdrawn method claims upon allowance of an elected product claim.

Information Disclosure Statement

To satisfy their continuing duties of candor and good faith, Applicants bring to the attention of the Examiner related subject matter in the patent applications, Serial Nos. 10/380,002, 10/557,586, and 12/933,390. The Examiner is invited to consider their prosecution histories and the prior art of record in those applications, which are accessible through the PTO's Image File Wrapper (IFW), in view of the Federal Circuit's holding in *McKesson Information Solutions v. Bridge Medical*, 82 USPQ2d 1865 (Fed. Cir. 2007). To avoid duplication of those materials in the PTO's records, reference to the IFW is encouraged but Applicants would be ready to submit copies of these materials for the Examiner's review if she prefers.

35 U.S.C. 112 – Definiteness

Claims 23, 37-39 and 44 were rejected under Section 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse because the claim amendments moot the rejections.

The recitations of amino acid residues by number and "one or more" are deleted.

The Examiner's suggestion to recite "said fusion protein" is adopted.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the cited disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A fact-finder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a

reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 23, 37-39 and 44 were rejected under Section 103(a) as allegedly being unpatentable over Colombo et al. (J. Immunol. 160:2780-2785, 1998) in view of Colombo et al. (Int'l Arch. Allergy Immunol., 130: 173-179, 2003), Bonura et al. (Int'l Arch. Allergy Immunol. 126:32-40, 2001) and Pauli et al. (Clin. Exp. Allergy 30:1076-1084, 2000). Applicants traverse because the fusion protein consisting of the amino acid sequence SEQ ID NO: 4 excludes trimeric forms such as disclosed by Pauli.

If a modification proposed by the Examiner would render a prior art invention inoperable for its intended purpose, then the cited document effectively teaches away from the proposed modification and fails to establish a prima facie case of obviousness. See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Here, the modification proposed in the Office Action would change the principle of operation of Pauli. Thus, the cited combination of documents fails to establish a prima facie case of obviousness. See *In re Ratti*, 123 USPQ 349 (CCPA 1959). Therefore, Pauli cannot be relied upon to establish a case of prima facie obviousness.

Finally, the Examiner is required to consider whether the improvement obtained by the present invention is more than the predictable use of prior art elements according to their established functions. See *KSR* at 1396. In Applicants' invention, the effects of the claimed heterodimer (PjEDcys) of the amino acid sequence SEQ ID NO: 4 derives from both (i) elimination of some disulphide bridges in Parj1 and Parj2 and (ii) assembly of the two modified allergens into a hybrid dimeric protein (i.e., the fusion contains two different modified allergens). The effects demonstrated in Applicants' specification would not have been predicted from the prior art. The documents cited in the Office Action (and especially not Pauli) do not make obvious Applicants' claimed heterodimer (cf. the statement on page 13 of the Office Action that

"comprising" does not exclude the use of a trimer). Here, a trimeric protein is excluded from the scope of the present claims.

The relevant inquiry for the obviousness determination is not whether *dimerization* or *trimerization* as described by Pauli **could** be applied to other allergens, but whether *dimerization* **would** be applied to Parj allergens. In other words, would it have been obvious for one of ordinary skill in the art from Pauli to consider a dimer of modified Parj allergens as a candidate for hypoallergenic immunotherapy? The conclusion would be NO! In fact, Pauli does not describe dimers and trimers as equivalent. On the contrary, the cited disclosure clearly shows that the dimer proved more allergenic in the skin pick test (see page 1082 of Pauli). Thus, a dimer is more likely to give uncontrolled allergic reactions upon injection.

For the foregoing reasons, Pauli **excluded** from their skin test the rBetv1 dimer and used the trimer only. Therefore, Pauli's disclosure when considered in its entirety teaches away from the claimed fusion protein, which is a heterodimer. In other words, one of ordinary skill in the art would not have found it obvious to use the claimed fusion protein over a trimeric protein with a reasonable expectation of success.

The dependent claims are also patentable over the combined disclosures do not render obvious all limitations of independent claim 23. In other words, claims 37-39 and 44 are not obvious from the cited documents because the limitations of an independent claim are incorporated in its dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Claims 23, 37-39 and 44 were rejected under Section 103(a) as allegedly being unpatentable over Vrtala et al. (FASEB J. 15:2045-2047, 2001) in view of Colombo et al. (Int'l Arch. Allergy Immunol., 130:173-179, 2003), Colombo et al. (J. Immunol. 160:2780-2785, 1998), and Bonura et al. (Int'l Arch. Allergy Immunol. 126:32-40, 2001). Applicants traverse

because the fusion protein consisting of the amino acid sequence SEQ ID NO: 4 excludes trimeric forms such as disclosed by Vrtala.

If a modification proposed by the Examiner would render a prior art invention inoperable for its intended purpose, then the cited document effectively teaches away from the proposed modification and fails to establish a prima facie case of obviousness. See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Here, the modification proposed in the Office Action would change the principle of operation of Vrtala. Thus, the cited combination of documents fails to establish a prima facie case of obviousness. See *In re Ratti*, 123 USPQ 349 (CCPA 1959). Therefore, Vrtala cannot be relied upon to establish a case of prima facie obviousness.

Finally, the Examiner is required to consider whether the improvement obtained by the present invention is more than the predictable use of prior art elements according to their established functions. See *KSR* at 1396. In Applicants' invention, the effects of the claimed heterodimer (PjEDcys) of the amino acid sequence SEQ ID NO: 4 derives from both (i) elimination of some disulphide bridges in Parj1 and Parj2 and (ii) assembly of the two modified allergens into a hybrid dimeric protein (i.e., the fusion contains two different modified allergens). The effects demonstrated in Applicants' specification would not have been predicted from the prior art. The documents cited in the Office Action (and especially not Vrtala) do not make obvious Applicants' claimed heterodimer (cf. the statement on page 19 of the Office Action that "comprising" does not exclude the use of a trimer). Here, a trimeric protein is excluded from the scope of the present claims.

The advantages related to preparation or formulation of the claimed fusion protein are discussed at page 5, lines 12-15, and page 7, lines 12-18 of Applicants' specification. Additional advantages are discussed below.

The relevant inquiry for the obviousness determination is not whether *dimerization* or *trimerization* as described by Vrtala **could** be applied to

other allergens, but whether *dimerization* **would** be applied to Parj allergens. In other words, would it have been obvious for one of ordinary skill in the art from Vrtala to consider a dimer of modified Parj allergens as a candidate for hypoallergenic immunotherapy? The conclusion would be NO! In fact, Vrtala does not describe dimers and trimers as equivalent. On the contrary, the cited disclosure clearly shows that the dimer is much less effective than the trimer in skin reaction tests (see page 2045 of Vrtala).

For the foregoing reasons, Vrtala **excluded** from their skin test the rBetv1 dimer and used the trimer only. Therefore, Vrtala's disclosure when considered in its entirety teaches away from the claimed fusion protein, which is a heterodimer. In other words, one of ordinary skill in the art would not have found it obvious to use the claimed fusion protein over a trimeric protein with a reasonable expectation of success.

The dependent claims are also patentable over the combined disclosures do not render obvious all limitations of independent claim 23. In other words, claims 37-39 and 44 are not obvious from the cited documents because the limitations of an independent claim are incorporated in its dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

It appears the Examiner contends that oligomerization of allergen would have reduced its IgE binding capacity. But this is incorrect in general. She tries to relate the hypoallergenic effects back to the decreased IgE binding of the hybrid construct, but this is contradicted by Pauli teaching at page 1081, "By contrast, the oligomeric forms of Betv1 (rBetv1 dimer and trimer) **retained IgE-binding capacity**" (emphasis added) and hypothesizes a different mechanism of action. Pauli also manifests surprise in finding that although the oligomers "retained the IgE binding capability, . . . unexpectedly, [they] exhibited a greatly reduced capability to induce basophil histamine release" at page 1077.

This lack of knowledge about the mechanism making an allergen construct hypoallergenic and the awareness that this effect was not mediated by a reduced IgE binding capacity, as alleged by the Examiner, is confirmed by Vrtala who affirms, "We found that E. coli expressed rBetv1 monomer, dimer and trimer exhibited a comparable ability to bind IgE antibodies from allergic patients" at page 2045. As a consequence, Vrtala hypothesized possible explanations for the hypoallergenic effect (see page 2047), including "steric hindrances and unfavorable charge interactions" that are characteristics of the chemical structure of each specific allergen.

Under such circumstances, one of ordinary skill in the art would not have found it obvious to modify the disclosures of Pauli and Vrtala to chemically different allergens with a reasonable expectation of success to achieve the desired effects of Applicants' invention and its claimed fusion protein.

Applicants request withdrawal of the Section 103 rejections because the claims would not have been obvious to one of ordinary skill in the art when this invention was made with a reasonable expectation of success.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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